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Sensitivity analysis for trend tests: application to the risk of radiation exposure

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SUMMARY

Trend tests are used to assess the relationship between multiple level treatment X and binary response R. In observational studies, however, there may be a confounder U that is associated with treatment X and causally related to response R. When the data for the confounder U are not observed, an approach for assessing the sensitivity of test results to U is provided. Its use is illustrated by examining data from a study of mutation rate after the Chernobyl accident.

Keywords: Omitted variable; Sensitivity analysis; Trend test.

1. INTRODUCTION

In dose–response studies, the experimental subjects are exposed to one of several dose levels of the chemical compound under investigation. The main objective is to determine whether the response rates increase with the dose levels. The data from a typical dose–response study can be summarized in a single $2 \times J$ contingency table (Table 1). Here x_j, $j = 1, \ldots, J$ are the scores assigned to the J levels of the treatment (dose), where x_1 is the minimum level or the level for the control group. Let n_j denote the number of subjects at the j-th level and π_j the corresponding response rate. The total number of subjects $N = \sum n_j$. The number of positive responses, Y_j, has a binomial distribution $B(n_j, \pi_j)$ and the Y_j, $j = 1, \ldots, J$, are independent. Cochran (1954) and Armitage (1955) proposed a test of monotonically increasing trend, where the null hypothesis is

$$H_0: \quad \pi_1 = \pi_2 = \cdots = \pi_J$$

and the alternative is increasing trend

$$H_1: \quad \pi_1 \leqslant \pi_2 \leqslant \cdots \leqslant \pi_J,$$

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Table 1. *Dose level and number of positive responses*

Dose level	x_1	...	x_j	...	x_J
Number of subjects for each dose level	n_1	...	n_j	...	n_J
Number of positive responses	Y_1	...	Y_j	...	Y_J

with at least one strict inequality. The standardized Cochran–Armitage (CA) test statistic is

$$Z_{\mathrm{CA}} = \frac{T}{\left[\widehat{\mathrm{Var}}(T)\right]^{\frac{1}{2}}} = \frac{\sum_{j=1}^{J} x_j (Y_j - n_j \hat{\pi})}{\left[\hat{\pi}(1-\hat{\pi}) \sum_{j=1}^{J} n_j (x_j - \bar{x})^2\right]^{\frac{1}{2}}}, \tag{1.1}$$

where $\hat{\pi} = \sum_{j=0}^{J} Y_j / \sum_{j=1}^{J} n_j$ and $\bar{x} = \sum_{j=1}^{J} n_j x_j / \sum_{j=1}^{J} n_j$. This test statistic is in the class of $C(\alpha)$ statistics discussed by Cox and Hinkley (1974, pp. 323–325). Under H_0, Z_{CA} has an asymptotic standard normal distribution for large n_j. Typically, the response probabilities $\pi = (\pi_1, \pi_2, \ldots, \pi_J)$ are modeled as $\pi_j = H(\alpha + \beta x_j)$, where $H(\cdot)$ is a monotone, twice differentiable function. Cox (1958) showed that CA trend test is the large sample approximation to the uniformly most powerful unbiased test against alternatives for any such $H(\cdot)$ function.

In observational studies, an apparent association between exposure X and response R may arise from an confounding variable U, the true causal agent, which is simultaneously related to the exposure. In this situation, the trend test of the association for Table 1 would then be misleading. Cornfield *et al.* (1959), Gastwirth (1988, 1992), Gastwirth *et al.* (1998), Rosenbaum and Krieger (1990), Rosenbaum and Rubin (1983) and Rosenbaum (2002) discussed sensitivity analysis with unobserved variables in various settings. In dose–response studies, there are multiple dose levels and it is natural to model the conditional distribution of U given the dose level X. In this paper, we extend the technique of sensitivity analysis to the trend test in $2 \times J$ tables and apply it to data sets from epidemiologic studies. The analysis complements that of Rosenbaum (2003) who considered exposures that were measured on a continuous scale.

2. SENSITIVITY OF TREND TESTS TO AN UNOBSERVED VARIABLE

If one had observed the complete data, i.e. the treatment X, the response R and the confounder U, an unbiased estimate of the treatment effect is obtained by controlling for U. The response probability is usually modeled by a logistic regression,

$$\pi(U, X) = P(R = 1 | U, X) = \frac{\exp(\alpha + \beta X + \gamma U)}{1 + \exp(\alpha + \beta X + \gamma U)}. \tag{2.1}$$

The effects of X and U on the response R are indicated by β and γ, which are called "strength" parameters. The test of interest is that whether the treatment has no effect on the response, i.e. H_0: $\beta = 0$. When the variable U is unobserved or omitted from the analysis, we only observe the data shown in Table 1 and fit the reduced logistic model

$$\pi^*(X) = \frac{\exp(\alpha^* + \beta^* X)}{1 + \exp(\alpha^* + \beta^* X)}. \tag{2.2}$$

The apparent effect of X is measured by β^* and the CA test (1.1) is actually testing the hypothesis H_0: $\beta^* = 0$. When U is a confounder, the test would be biased for testing whether there is a treatment effect H_0: $\beta = 0$.

In order to adjust the trend test for the effect of U, the association between U and X should be considered. If we know the conditional distribution of the unobserved variable U given the treatment

level x_j, e.g. the proportion $w_{u|j} = P(U = u|X = x_j)$ if U is categorical or the density $f(u|x_j)$ if U is continuous, we can incorporate such information to calculate the marginal response probabilities $P(R = 1|X = x_j)$. Otherwise, we may assume a range of possible models for the association between the unobserved variable and the treatment. The association is modeled by the conditional distribution of U given the level of X (Rosenbaum, 1989)

$$f(u|x) = \exp[\tau(x) + \xi(u) + \delta ux], \tag{2.3}$$

where $\xi(u)$ is an unknown function, $\tau(x)$ is a normalizing constant. If $\delta \neq 0$, X and U are not independent, and the 'imbalance' parameter δ indicates the association between X and U.

According to model (2.3), U can be either a categorical or a continuous variable. When U is an ordinal categorical variable taking values $0, \ldots, K$, then $\tau(x) = -\log\{\sum_{u=0}^{K} \exp(\xi(u) + \delta xu)\}$ and

$$f(u|x) = P(U = u|X = x) = \frac{\exp(\lambda_u + \delta xu)}{1 + \sum_{k=1}^{K} \exp(\lambda_k + \delta xk)}, \quad u = 0, \ldots, K, \tag{2.4}$$

where $\lambda_k = \xi(k) - \xi(0)$, $k = 0, \ldots, K$. When $K = 1$, U is a binary variable. Model (2.3) also applies when U is normally distributed. Then $\tau(x) = -\frac{1}{2}(\lambda + \delta x)^2$, $\xi(u) = \lambda u - \frac{1}{2}u^2 - \frac{1}{2}\log(2\pi)$ and

$$f(u|x) = \phi(u|\lambda + \delta x, 1), \tag{2.5}$$

where $\phi(\cdot|a, b)$ is the density function of a normal distribution with mean a and variance b.

Because the confounder U is omitted, we only observe the marginal response probabilities at dose level x_j, $P(R = 1|X = x_j, \beta)$. These observed probabilities, denoted by $\pi_j^{(\beta)}(\gamma, \delta)$, $j = 1, \ldots, J$, depend on the true treatment effect β as well as the 'imbalance' parameter δ and 'strength' parameter γ. For simplicity of exposition, we write them as $\pi_j^{(\beta)}$. Thus, the response probabilities under the null hypothesis H_0: $\beta = 0$ are denoted by $\pi_j^{(0)}$.

2.1 *Some properties of $\pi_j^{(\beta)}$ and Z_{CA} when the confounder U is omitted*

If the unobserved confounder U is a categorical variable, the response probability at level x_j

$$\pi_j^{(\beta)} = \sum_{u=0}^{K} P(R = 1|X = x_j, U = u)P(U = u|X = x_j). \tag{2.6}$$

When U is continuous with density $f(u|x_j)$ at level x_j, then

$$\pi_j^{(\beta)} = \int_{-\infty}^{\infty} P(R = 1|X = x_j, U = u)\, f(u|x_j)\, \mathrm{d}u. \tag{2.7}$$

Because U is not observed, the likelihood for the observed $2 \times J$ contingency table is

$$L\left(\pi_1^{(\beta)}, \ldots, \pi_J^{(\beta)} | X, Y\right) = \prod_{j=1}^{J} \binom{n_j}{Y_j} \left(\pi_j^{(\beta)}\right)^{Y_j} \left(1 - \pi_j^{(\beta)}\right)^{n_j - Y_j}. \tag{2.8}$$

Next, we prove a theorem about the observed response probabilities $\pi_j^{(0)}$ under the null hypothesis H_0: $\beta = 0$ and show how the distribution of Z_{CA} is affected by the unobserved variable U. The proofs of the theorems are posted on the journal web site.

THEOREM 2.1 Assume that the response probability satisfies model (2.1) and the relationship between unobserved confounder U and treatment X is modeled by (2.3). If $\gamma\delta > 0$, the observed response probabilities $\{\pi_j^{(0)}, j = 1, \ldots, J\}$ under the null H_0: $\beta = 0$ satisfy

$$\pi_1^{(0)} < \cdots < \pi_j^{(0)} < \cdots < \pi_J^{(0)}.$$

THEOREM 2.2 If U is a confounder, i.e. $\delta\gamma \neq 0$, the CA test is no longer unbiased. The asymptotic distribution of the CA trend test statistics Z_{CA} is

$$P(Z_{\mathrm{CA}} \leqslant t) = \Phi\Big(\frac{s_0 t - B_\beta}{\sigma_\beta}\Big), \tag{2.9}$$

where $s_0 = [\hat{\pi}(1-\hat{\pi})\sum_{j=1}^J n_j(x_j-\bar{x})^2]^{\frac{1}{2}}$ only depends on observed data and $B_\beta = \sum_{j=1}^J n_j \pi_j^{(\beta)}(x_j - \bar{x})$ and $\sigma_\beta = [\sum_{j=1}^J \pi_j^{(\beta)}(1-\pi_j^{(\beta)})n_j(x_j-\bar{x})^2]^{\frac{1}{2}}$ depend on observed data as well as the parameters (β, δ, γ).

REMARK 1 Under null hypothesis of no exposure effect, the equality of marginal response probabilities $\pi_1^{(0)} = \cdots = \pi_J^{(0)}$ is true only when $\delta\gamma = 0$, i.e. the omitted variable U is not a confounder. In this case, $B_0 = 0$ and the limiting distribution of Z_{CA} is standard normal $\Phi(t)$.

REMARK 2 When $\delta\gamma \neq 0$, the CA test is no longer unbiased as $B_0 \neq 0$ according to Theorem 2.1. When $\delta\gamma > 0$, the observed data show spurious positive effect under the null hypothesis.

REMARK 3 In the asymptotic distribution (2.9), B_β is of order N when $\pi_j^{(\beta)}$ are not all equal and s_0 and σ_β are of order $\sqrt{N}$. A simple example is helpful. Let $x_i = i$ and $n_i = N/3$, $i = 1, 2, 3$. Then $\bar{x} = 2$ and $s_0 = [2\hat{\pi}(1-\hat{\pi})N/3]^{\frac{1}{2}}$ is of order $\sqrt{N}$. If a confounder is omitted, then $\pi_1^{(\beta)} \neq \pi_3^{(\beta)}$. Hence, $B_\beta = (\pi_3^{(\beta)} - \pi_1^{(\beta)})N/3$ is of order N and $\sigma_\beta = \{[\pi_1^{(\beta)}(1-\pi_1^{(\beta)}) + \pi_3^{(\beta)}(1-\pi_3^{(\beta)})]N/3\}^{\frac{1}{2}}$ is of order $\sqrt{N}$. Similar to the Pitman efficiency, when the local alternatives β_k converge to the null value 0 slowly, say like $1/\log\log n$, the limiting distribution of Z_{CA} is no longer a standard normal, but a normal distribution with non-zero mean, because of confounding; when the alternative $\beta > 0$ stays fixed as $N \to \infty$, the power goes to 1.

REMARK 4 If we use the rejection region $\{Z_{\mathrm{CA}} > Z_{1-\alpha}\}$, the true significance level and true power of the test are $1 - \Phi(\frac{s_0 Z_{1-\alpha} - B_0}{\sigma_0})$ when the exposure has no effect, i.e. H_0: $\beta = 0$. Let z_{CA} be the observed value of the CA trend test statistic Z_{CA}, the true p-value and power of the one-sided trend test are $1-\Phi(\frac{s_0 z_{\mathrm{CA}} - B_0}{\sigma_0})$ and $\Phi(\frac{s_0 z_{\mathrm{CA}} - B_\beta}{\sigma_\beta})$, respectively. The power under the non-null case is useful when one designs a study or calculates the power when a confounder is omitted. Yu and Gastwirth (2003) assessed the power for the test of independence in a 2×2 table for the study of the spermicide effect on birth defects.

2.2 *Sensitivity analysis for the CA trend test*

Because an unobserved confounder may introduce a spurious treatment effect, thereby biasing the trend test, it is desirable to assess the sensitivity of the test result under *plausible* assumptions about the effect of X and U on the response R and the association between U and X. The relationship between R and (X, U) is specified by the "strength" parameters β and γ, respectively, in model (2.1). The association between U and X is specified by conditional distribution $f(u|x)$. Let $\omega = (\omega_{u|1} = P(U = u|x = x_1), u = 0, \ldots, K)$ if U is categorical and ω be the mean of U at exposure level x_i if U is continuous.

If the conditional distribution of U given X is modeled by (2.4) or (2.5), the distribution is specified by the "imbalance" parameters (ω, δ) (Appendix 4). The observed response probabilities $\pi_j^{(\beta)}$ at exposure level x_j depend on both the "imbalance" parameters (ω, δ) and the "strength" parameters (β, γ). For fixed plausible values of $(\omega, \delta, \beta, \gamma)$, the maximum likelihood estimates (MLEs) of $\pi_j^{(\beta)}$ can be obtained from the likelihood (2.8). The estimates of B_β and σ_β in (2.9) will be obtained by substituting $\hat{\pi}_j^{(\beta)}$ for $\pi_j^{(\beta)}$. Appendix 4 shows how to obtain the MLE of $\pi_j^{(\beta)}$ given the distribution of U conditioning on X.

By changing the values of the parameters $(\omega, \delta, \beta, \gamma)$, we are able to assess the sensitivity of the trend test Z_{CA} to the unobserved variable U. The true p-value for testing H_0: $\beta = 0$ can be calculated as $1 - \Phi(\frac{s_0 z_{\mathrm{CA}} - \hat{B}_0}{\hat{\sigma}_0})$ and the power under H_1: $\beta > 0$ can be estimated as $\Phi(\frac{s_0 z_{\mathrm{CA}} - \hat{B}_\beta}{\hat{\sigma}_\beta})$.

3. Application

We apply the sensitivity analysis to a study of the risk of radiation exposure. The study investigates the human minisatellite mutation rate after the Chernobyl accident (Dubrova, 1996). It has long been known that high levels of radiation cause mutations—typically chromosomal breaks. However, there is little evidence that ionizing radiation increases the general germline mutation rates for all genes in humans. Examination of mutations at minisatellite loci, which have a high base mutation rate, provides a more powerful assay of mutation rate and makes it possible to detect a statistically significant increase in mutation rate in a relative small sample size. For example an increase in germline mutation rate for minisatellites with exposure to radiation has been demonstrated in mice (Dubrova *et al*., 1993).

The largest reported accidental release of radioactivity in history occurred at the Chernobyl nuclear power station in Belarus on April 26, 1986. To determine its effect on germline mutation rates, Dubrova *et al*. (1996) estimated the mutation rates for five minisatellite probes in children born to parents exposed to the Chernobyl radiation and compared them to rates in matched, unexposed British families. For the families in which all probes were scored, the control group had 23 mutations in 1491 scored bands, whereas the exposed group had 49 mutations in 1615 scored bands. The relative risk of exposure, 1.97, is statistically significant with p-value 0.004 obtained from Fisher's exact test.

In addition, when the Belarus families are grouped according to median Cesium surface contamination into those that experienced less contamination (surface contamination <6.8 Ci km^{-2}) and those that experienced more (>6.8 Ci km^{-2}), there is a statistically significant difference ($p = 0.041$) in estimated mutation rates (0.026 and 0.035 between the low and high contaminated populations, respectively; Table 2).

Because of the robustness of equally spaced scores, i.e. 0 for the control group, 1 and 2 for the low and high contamination groups are used for the CA trend test, which yields a more significant result ($p = 0.0014$) than Fisher's exact test. This increased trend indicates that the increase in mutation frequency among offspring of irradiated parents may be a direct consequence of radiation exposure.

However, Kodaria *et al*. (1995) carried out a similar study in children from families exposed to atomic bomb radiation in Japan. In contrast to Dubrova *et al*. (1996), they found very similar mutation rates in exposed and control samples for the same minisatellites (12 mutations in 1111 bands for the exposed group and 13 mutations in 1111 bands for the control group). Kodaira *et al*. (1995) suggested that a comparison to a more appropriate matched control group is necessary to properly evaluate the effect of radiation on human mutation rates. Furthermore, other non-radioactive contaminants from Chernobyl, such as heavy metals, could be responsible for the observed, apparently dose-dependent increase in mutation rate.

Although one can no longer collect data about possible confounders, we can assess how sensitive the conclusion based on the dose–response data might be to potential confounding factors. We assume that another non-radioactive binary risk factor (U) is causally related to the mutation and associated with the radiation. First, we assume that there is an increasing trend in the prevalences of U in the control,

Table 2. ^{137}*Cesium surface contamination and mutation rate*

	Control	Low contamination	High contamination
Equal space score (X)	0	1	2
Scored bands (n)	1491	809	806
Mutations (Y)	23	21	28

low contamination and high contamination groups. Following the technique described in Section 2, the response probability follows model (2.1) and the association between X and U is specified in model (2.4) by the parameters (δ, ω).

We assume that the omitted factor is a risk factor that is more prevalent in the contaminated area and the parameter $\delta \in \{0.5, 1.0\}$. The prevalence of U in the control group is $\omega_{1|0} = \{0.01, 0.05, 0.10, 0.20\}$. The odds ratio of the confounder U is indicated by $\exp(\gamma)$. The prevalences of U in the exposure group are calculated using the parameters $(\delta, \omega_{1|0})$ (see Appendix A). The p-values of the trend test for various situations are summarized in Table 3. The last column shows the required odds ratio for $U(e^{\gamma})$ to raise the p-value to 0.05. Based on Table 3, the trend test is sensitive to a confounding factor of modest risk ($e^{\gamma} \geqslant 3$) which is not balanced across three groups. For example in Case 6, when the prevalence of U in the control group $\omega_{1|0} = 0.10$, the imbalance parameter $\delta = 1.0$ and the odds ratio of U is 3.0, the adjusted p-value is 0.096, which is not significant. This means that the finding that ionizing radiation increases the general germiline mutation rates could be questioned and the dose-dependent mutation rate found by Dubrova *et al.* (1993) might be due to another factor.

Notice, however, that the requirement that the prevalences of U increase in the same order across the three groups is a strong one. Following the suggestion by Kodaira *et al.* (1995), it may be more reasonable to assume that the prevalence of U is the same in both exposed groups, i.e.

$$f = Pr(U = 1|X = 1 \text{ or } 2) > Pr(U = 1|X = 0) = \omega_{1|0}.$$

Table 4 presents a sensitivity analysis based on the assumption that the prevalence of U in both exposed groups, f, is the same and exceeds its prevalence, $\omega_{1|0}$, in the control (British) group. To be comparable

Table 3. *The p-values of the trend test with different values of (ω, δ, γ) for the unobserved variable and required odds ratio of U to raise the p-value to* 0.05

Case	δ	Prevalences of confounder U				Odds ratio of U: $\exp(\gamma)$				Required odds ratio for $p = 0.05$
		Control	Low	High	Average	1.5	3	6	9	
		$\omega_{1\|0}$	$\omega_{1\|1}$	$\omega_{1\|2}$	f	Adjusted p-value				
1	0.5	0.01	0.02	0.02	0.02	0.002	0.002	0.003	0.004	84.5
2	1.0	0.01	0.03	0.07	0.05	0.002	0.005	0.017	0.040	10.0
3	0.5	0.05	0.08	0.13	0.11	0.002	0.006	0.022	0.047	9.3
4	1.0	0.05	0.13	0.29	0.21	0.005	0.047	0.280	0.526	3.1
5	0.5	0.10	0.15	0.23	0.19	0.003	0.011	0.046	0.090	6.3
6	1.0	0.10	0.23	0.45	0.34	0.008	0.096	0.423	0.644	2.5
7	0.5	0.20	0.29	0.40	0.34	0.004	0.020	0.068	0.113	4.9
8	1.0	0.20	0.40	0.63	0.51	0.010	0.112	0.376	0.530	2.3

Table 4. *The p-values of the trend test with different prevalences of the omitted risk factor in the control and exposed groups and the required odds ratio of U to raise the p-value to* 0.05

Case	Prevalence of U		Odds ratio of U: $\exp(\gamma)$				Required odds ratio for $p = 0.05$
	Control	Exposed	1.5	3	6	9	
	$\omega_{1\|0}$	f	Adjusted p-value				
1	0.01	0.02	0.001	0.002	0.002	0.003	258.4
2	0.01	0.05	0.002	0.003	0.008	0.016	17.0
3	0.05	0.11	0.002	0.004	0.012	0.023	15.1
4	0.05	0.21	0.003	0.020	0.111	0.239	4.3
5	0.10	0.19	0.002	0.007	0.021	0.039	10.8
6	0.10	0.34	0.005	0.041	0.192	0.341	3.2
7	0.20	0.34	0.003	0.011	0.034	0.054	8.4
8	0.20	0.51	0.006	0.054	0.194	0.297	2.9

with the results in Table 3, we assume that $(n_1+n_2)\,f = n_1\omega_{1|1}+n_2\omega_{1|2}$, where n_1 and n_2 are the number of scored bands from the exposed families in both low and high contamination groups.

Comparing Tables 3 and 4, we see that if the prevalences of risk factor U increase with contamination level, the trend test is more sensitive than when U has equal prevalence in both contamination groups. For example for Case 6, if $\omega_{1|0} = 0.10$ and $\exp(\gamma) = 3$, the p-values of the trend test are 0.096 and 0.041 in Tables 3 and 4, respectively. Thus, the proper sensitivity model may depend on subject matter considerations.

4. Discussion

The paper utilizes an approach similar to that of Rosenbaum (2002) to develop a sensitivity analysis for testing data for a dose–response or trend. The main difference from previous approaches (Rosenbaum and Rubin, 1983; Rosenbaum, 2002) is that we follow Cornfield *et al.* (1959) who consider the conditional distribution of the unobserved variable U given the dose or exposure level X, rather than the propensity score. The method is illustrated on a data set concerned with the effect of radiation. In the case of the Chernobyl accident, the model of association between the unobserved confounder U and the exposure level X is shown to have a substantial impact on the sensitivity analysis.

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APPENDIX A

Conditional distribution of U given X is specified by (ω, δ) when the association model is (2.4) or (2.5)

When U is a categorical variable, the conditional distribution of U given X is specified by $\{\omega_{u|j}, u = 0, \ldots, K,\ j = 1, \ldots, J\}$ and $\omega = (\omega_{0|1}, \ldots, \omega_{K|1})$ are the distribution of U at exposure level x_1. Model (2.4) implies that

$$\omega_{u|1} = P(U = u|X = x_1) = \frac{e^{\lambda_u+\delta x_1}}{1+\sum_{k=1}^{k} e^{\lambda_k+\delta x_1}}, \quad u = 1, \ldots, K.$$

Hence, $\lambda_u = \log(\frac{\omega_{u|1}}{\omega_{0|1}}) - \delta x_i$ and $\omega_{u|j}$ can be obtained by plugging λ_u into (2.4). When U is binary, $\lambda_1 = \log(\frac{\omega_{u|1}}{1-\omega_{u|1}})$.

When U is normal, the conditional distribution of U given X is $\phi(\lambda+\delta x, 1)$ and ω is the mean of U at exposure level x_i. Hence, $\lambda = \omega - \delta x_1$ and the conditional distribution is $f(u|x_j) = \phi(\omega+\delta(x_j - x_1), 1)$.

APPENDIX B

Maximum likelihood estimation of $\pi_j^{(\beta)}$ given the conditional distribution $\omega_{u|j} = P(U = u|X = x_j)$ or $f(u|x_j)$

The loglikelihood for the observed $2 \times J$ table from the dose–response study is

$$\ell\left(\pi_1^{(\beta)}, \ldots, \pi_J^{(\beta)}|X, Y\right) = \sum_{j=1}^{J} \log\left(\frac{n_j!}{Y_j!(n_j - Y_j)!}\right) + \sum_{j=1}^{J} \left\{Y_j \log \pi_j^{(\beta)} + (n_j - Y_j)\log(1 - \pi_j^{(\beta)})\right\}.$$

The response rates $\{\pi_j^{(\beta)},\ j = 1, \ldots, J\}$ are functions of α for fixed values of (β, γ) and known distribution $f(u|x_j)$. The MLE of α can be obtained by solving

$$\frac{\partial \ell(\pi_1^{(\beta)}, \ldots, \pi_J^{(\beta)}|X, Y)}{\partial \alpha} = \sum_{j=1}^{J} \frac{\partial \pi_j^{(\beta)}}{\partial \alpha}\left(\frac{Y_j}{\pi_j^{(\beta)}} - \frac{n_j - Y_j}{1 - \pi_j^{(\beta)}}\right) = 0. \tag{B.1}$$

The MLEs of $\pi_j^{(\beta)}$, $\hat{\pi}_j^{(\beta)}$ are obtained by plugging $\hat{\alpha}$ into (2.6) or (2.7).

If U is categorical, the distribution of U conditioning on X is given by $\{\omega_{u|j}, u = 0, \ldots, K,\ j = 1, \ldots, J\}$. Hence,

$$\frac{\partial \pi_j^{(\beta)}}{\partial \alpha} = \sum_{u=0}^{K} (1 - \omega_{u|j}) \frac{e^{\alpha+\beta x_j+\gamma u}}{(1 + e^{\alpha+\beta x_j+\gamma u})^2}.$$

If U is continuous with conditional distribution $f(u|x_j)$, then

$$\frac{\partial \pi_j^{(\beta)}}{\partial \alpha} = \int_{-\infty}^{\infty} \frac{e^{\alpha+\beta x_j+\gamma u}}{(1 + e^{\alpha+\beta x_j+\gamma u})^2} f(u|x_j)\, du.$$

In both situations, it can be shown that

$$\lim_{\alpha\to-\infty} \pi_j^{(\beta)} = \lim_{\alpha\to-\infty} \frac{\partial \pi_j^{(\beta)}}{\partial \alpha} = \lim_{\alpha\to\infty} \frac{\partial \pi_j^{(\beta)}}{\partial \alpha} = 0 \text{ and } \lim_{\alpha\to\infty} \pi_j^{(\beta)} = \lim_{\alpha\to-\infty} \frac{\frac{\partial \pi_j^{(\beta)}}{\partial \alpha}}{\pi_j^{(\beta)}} = \lim_{\alpha\to\infty} \frac{\frac{\partial \pi_j^{(\beta)}}{\partial \alpha}}{1 - \pi_j^{(\beta)}} = 1.$$

Hence,

$$\lim_{\alpha\to-\infty} \frac{\partial \ell(\pi_1^{(\beta)}, \ldots, \pi_J^{(\beta)}|X, Y)}{\partial \alpha} = \sum_{j=1}^{J} Y_j \quad \text{and} \quad \lim_{\alpha\to\infty} \frac{\partial \ell(\pi_1^{(\beta)}, \ldots, \pi_J^{(\beta)}|X, Y)}{\partial \alpha} = -\sum_{j=1}^{J} (n_j - Y_j).$$

Because $\lim_{\alpha\to-\infty} \frac{\partial \ell(\pi_1^{(\beta)}, \ldots, \pi_J^{(\beta)}|X,Y)}{\partial \alpha}$ is a polynomial function of e^{α}, hence is continuous in α, (B.1) always has a real solution. The maximum likelihood estimate of α can be obtained using MAPLE language $\hat{\alpha} :=$ fsolve$(\frac{\partial \ell}{\partial \alpha}, \alpha)$.

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